REMARKS/ARGUMENTS

I. Amendments to Specification

The amendments to Tables 1, 2, 4, 5 and 8 insert a sequence identifier for the elected nucleic acid corresponding to GenBank Accession No. M80634, a copy of which is enclosed for the convenience of the Examiner. The sequence entered into the Sequence Listing was submitted to GenBank in 1992. This amendment contains no new matter.

This amendment is accompanied by a floppy disk containing SEQ ID NO:1 in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

II. Support for Claim Amendments

Applicants thank the Examiner for the thoughtful comments and suggestions in the February 13, 2006 Office Action. As shown above, Applicants have canceled claims 2-29 without prejudice. Applicants reserve the right to pursue claims with scope equivalent to any of canceled claims 2-29 in the future.

Applicants have amended claim 1 in several respects. First, claim 1 has been amended to limit the claim to methods of determining whether a subject is *predisposed* (more likely than not) to have *major depression disorder*. Support for this amendment may be found in the claims as originally filed (*i.e.*, claim 8) and in the specification at, *e.g.*, Table 4. Second, claim 1 has been amended to recite the testing of *isolated brain tissue*, specifically *dorsolateral prefrontal cortex tissue*. Support for this amendment can be found in the specification at, *e.g.*, paragraphs 4, 5, 19, 52, and Table 4.

Claim 1 has also been amended to recite a step of associating a "*nucleic acid* reagent" to a "polynucleotide with 95% identity to SEQ ID NO:1." Support for this amendment is found in the specification, *e.g.*, at paragraph 67 (defining the terms, "identical" and "percent identity"); at paragraph 229 (describing microarray analysis using Affymetrix chips to detect genes identified in Table 4); and in the claims as originally filed (*e.g.*, claim 3).

Finally, claim 1 has been amended to recite the additional step of *comparing* detected levels of gene expression to control levels prior to making a determination based on the detected levels. Support for this amendment can be found in the specification at, *e.g.*, paragraph 224:

> Diagnosis involves determining the level of a polypeptide or polynucleotide of the invention in a patient and then comparing the level to a baseline or range. Typically, *the baseline value is representative of a polypeptide or polynucleotide of the invention in a healthy person not suffering from a mood disorder or psychotic disorder* or under the effects of medication or other drugs. Variation of levels of a polypeptide or polynucleotide of the invention from the baseline range (either up or down) indicates that the patient has a mood disorder or psychotic disorder or at risk of developing at least some aspects of a mood disorder or psychotic disorder.

(emphasis added); paragraph 229 (RNA levels compared using "matched controls") (emphasis added); paragraph 19 (Table 4 legend stating that "[u]p and down indicates the direction of the changes compared to controls"); and paragraph 37 ("Figure 14 shows RealTime PCR results which confirm that selected FGF-related genes first identified using microarray analysis are differentially expressed in mood disorders").

Applicants have also added new claim 30. Claim 30 is a dependent claim reciting the sampling of tissue from a *deceased* subject. Support for this new claim may be found in the specification at, *e.g.*, paragraphs 229. Thus, none of the forgoing amendments and additions to the pending claims add new matter.

III. Informal Objections to the Claims

On page 3 of the Office Action, the Examiner objected to the previously pending claims as encompassing non-elected subject matter. Applicants respectfully submit that their amendments to the claims have addressed this issue and request withdrawal of the objection.

IV. Rejection of Claims under 35 U.S.C. § 112, paragraph 1, enablement

The Examiner rejected claims 1, 3-4 and 6-10 under 35 U.S.C. § 112, paragraph 1 as non-enabled. See Office Action at page 3. Specifically, the Examiner states that "[t]he base claim [*i.e.*, claim 1] is very broad" and "[t]he specification does not provide enablement for

determining if a patient either has or is predisposed to a mood disorder." *Id.* at page 3. On page 4 of the Office Action, the Examiner writes:

> The only working example in the specification (p. 59) describes the results of experiments performed on post-mortem human tissue. Because the tissue was taken from patients who were already dead and already had been diagnosed with either major depression disorder (MDD) or bipolar disorder (BP), it was not possible to determine if the patients will develop either disorder, as the disease states of the dead do not progress."[1]

Applicants respectfully disagree with the Examiner. As an initial matter, Applicants note that the Examiner's arguments are largely mooted by Applicants' amendments to claim 1. Moreover, Applicants' specification enables the pending claims because postmortem brain expression patterns relate reasonably well to expression patterns in living brains and the techniques required to practice Applicants' invention do not require undue experimentation on the part of those skilled in the art (on the contrary, the techniques are standard).

While Applicants find no fault with the argument that dead people do not develop MDD or BP, Applicants respectfully submit that the Examiner has confused two issues. First, the claimed method is useful for determining, *e.g.*, in the context of a pathological examination, whether a deceased subject might have suffered from a major depression disorder. Second, the Examiner ignores the fact that skilled artisans recognize that conclusions drawn from post-mortem brain studies such as those described by Applicants are applicable to pre-deceased subjects.

With respect to this second issue, it is axiomatic that the enablement standard of 35 U.S.C. § 112 does not require Applicants to teach the skilled practitioner what the skilled practitioner already knows ("a patent need not teach, and preferably omits, what is well known in the art"). See MPEP 2164.01 (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Likewise, it is not necessary for Applicants' to specify every sub-step in the method(s) of practicing the invention if it is known to one skilled in the art that such information could be

[1] The Examiner likewise asserts on page 5 of the Office Action that, "'the specification ... is only enabling for *retrospective determination* if a patient had major depression." (emphasis added)

obtained without undue experimentation. See MPEP 2164.01(c); see also MPEP 2164.02 (citing *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970)).

Skilled artisans have long been aware that the study of post-mortem human brains provides information relevant to understanding the biology of the living subjects from whom the brains were isolated. This is why post-mortem studies have been and continue to be a recognized source of useful information for scientists and physicians. Applicants have attached to this Response publications showing the solid and predictable relationship between post-mortem and living brain tissue. For example, the Franz *et al.* reference shows that researchers' well-considered reliance on post-mortem brains was entirely justified:

> We found that despite the large impact that death as such and, potentially, surgery have on gene expression patterns in autopsy and resection samples, respectively, *differences between brain regions that exist in the living brain are mostly retained in postmortem samples*.

See Franz *et al.*, page 6, bottom of first column (emphasis added). Although Franz *et al.* found that a small portion of genes (roughly 10%) are consistently differentially expressed in living versus post-mortem brains, Franz *et al.* note that the differentially expressed genes are mostly:

> [g]enes involved in rather basic functions, such as RNA processing, protein biosynthesis and transport, organelle organization and biogenesis, the ubiquitin cycle, and DNA repair (Table 1) are over-represented among genes differently expressed between autopsies and resections.

See Franz *et al.*, page 6, middle of column 2. Applicants' claims do not involve the detection of the sort of "housekeeping" genes described by Franz *et al.* Rather, Applicants' claims are drawn to methods of detecting the expression of mRNA encoding FGFR2, a human keratinocyte growth factor receptor. See, *e.g.*, Table 1 of the specification. Thus, Franz *et al.* simply provide another confirmation of what neurologists have reasonably believed to be true for many years: studying post-mortem brains is a reliable method of obtaining information about living brains.

Applicants also provide a review published in the *Journal of Chemical Neuroanatomy* (Bahn *et al.*, "Gene expression profiling in the post-mortem human brain -- no cause for dismay," (2001) 22: 79-94) showing that skilled artisans have known for some time how to obtain post-

mortem brain samples that accurately reflected the *in vivo* state of the subjects from whom the samples were taken. The Bahn *et al.* abstract teaches that "post-mortem tissue undoubtedly is the fundamental prerequisite to investigate complex brain disorders with molecular profiling techniques." In the body of the publication, Bahn *et al.* teach further:

> [W]ith appropriate tissue preparation the structural integrity of post-mortem tissue can be preserved allowing for detailed morphological, morphometrical, and ultrastructural investigations e.g. (Benes, 1988); Ravid et al., 1992; Vonstattel et al., 1995; Waldvogel et al., 1999). . . . Furthermore, high throughput mRNA expression profiling is possible using post-mortem human brain tissue and data from our laboratories demonstrate that robust and reproducible results can be achieved . . . . *Post-mortem human brain material is a precious and valuable resource for molecular studies.*

See Bahn *et al.*, pages 79-80 (emphasis added).[2]

The Federal Circuit has held that Applicants are required to show that the art recognizes a *reasonable* correlation between a model (e.g., post-mortem brains) and the claimed method, not a "rigorous" or "invariable" correlation. *See Cross v. Itzuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also* MPEP 2164.02. Applicants have provided evidence which satisfies this requirement. In addition, Applicants' specification shows that subjects with MDD are significantly more likely to exhibit reduced levels of FGFR2 mRNA expression. Applicants' novel assay exploits this relationship to provide a means for determining an increased likelihood that a subject is predisposed to MDD, or that a subject was suffering from MDD prior to death.

Applicants note that the sort of information provided by Applicants' novel assay is especially useful because many bipolar patients who seek treatment and/or analysis of their condition do so only when depressed. Thus, objective biological criteria for distinguishing between bipolar disorder and MDD are useful to mental health clinicians, who otherwise might be confused by the similar psychological symptoms displayed by treatment-seeking subjects.

V. Rejection of Claims under 35 U.S.C. § 112, paragraph 1, written description

[2] The complete citations for the references in the quoted passage from Bahn *et al.* follow: Benes F.M. (1988) *Psychiatr. Dev.*, 6:213–226; Ravid R. *et al.* (1992) *Prog. Brain. Res.*, 93:83–95; Vonsattel J.P. *et al.* (1995) *J. Neuropathol. Exp. Neurol.*, 54:42–56; Waldvogel H.J. *et al.* (1999) *J. Comp. Neurol.*, 415:313–340.

On pages 6-7 of the Office Action, the Examiner rejected claim 1 and claims 3-4 for failing to meet the written description requirement of 35 U.S.C. § 112, paragraph 1. With respect to claim 1, the rejection was based on the breadth of the terms "reagent" and "mood disorder." Claim 1 has been amended and Applicants respectfully submit that the amendments render the Examiner's written description arguments with respect to these terms moot.

With respect to claims 3-4, the Examiner argued that the specification failed to provide adequate written description support for the "nucleic acids and molecules which associate with nucleic acids . . .in a generic way." The Examiner argues that "[t]here is no requirement in either claim 3 or 4 that either the nucleic acid or polynucleotide have any particular structure or function." Claims 3-4 have been canceled and Applicants respectfully submit that the structure and function of the nucleic acids and polynucleotides in claim 1 are specified with sufficient particularity to meet the written description requirements of 35 U.S.C. § 112, paragraph 1. Applicants respectfully request withdrawal of the rejection.

VI. Rejection of Claims under 35 U.S.C. § 112, paragraph 2

The Examiner rejected claims 1, 3-4, and 6-10 under 35 U.S.C. § 112, paragraph 2, as indefinite based on the recitation of the terms "stringent conditions" and "selectively associates." See Office Action at pages 7-8. Applicants' pending claims no longer recite the term "stringent conditions" so the Examiner's rejection is moot with respect to that term.

With respect to the term, "selectively associates," the Examiner states that the "term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." *Id.* at page 8.

Applicants respectfully disagree. In light of the claim language and Applicants' teaching in the specification, the meaning of the term "selectively associates" is clear to one of skilled in the art. Applicants' claims, as amended, are drawn to a method for determining the levels of expression of a specific mRNA -- *i.e.,* the mRNA encoding the FGFR2 receptor -- and correlating below-normal levels with an increased likelihood that the subject is or was predisposed to MDD. In this context, the term "selectively associates" clearly refers to an easily

measurable property of a nucleic acid, *i.e.*, a binding affinity for FGFR2 mRNA which provides specificity sufficient to allow a skilled artisan to accurately determine the levels of expressed FGFR2 mRNA.

The techniques required to identify and optimize FGFR2-specific nucleic acids for use in Applicants' claimed assay are well-known. The experimentation required to identify such nucleic acids is routine. The standard widely-recognized steps involved in the process of selecting and troubleshooting methods of nucleic acid hybridization are described in Applicants' specification at pages 28-32 ("IV. Detection of Gene Expression").

Applicants teach in the specification at paragraph 114 that "the selection of a nucleic acid hybridization format is not critical." Indeed, *any* nucleic acid which selectively associates with FGFR2 mRNA and thus allows FGFR2 mRNA expression to be measured with a reasonable degree of confidence will be suitable use in Applicants' claimed assay. The fact that Applicant does not identify each and every possible nucleic acid composition that could be used in Applicants' claims does not render Applicants' claims "indefinite." Applicants are not claiming a nucleic acid *composition*. Applicants are claiming an assay for obtaining information related to a subject's mental health and, in light of the specification, the scope of the claims is clear. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, paragraph 2.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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Attachments
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Attachments:

1. GenBank Accession No. M80634;

2. Bahn, *et al.,* Gene expression profiling in the post-mortem human brain - no cause for dismay; Journal of Chemical Neuroanatomy 22 (2001) 79-94;

3. Franz, *et al.,* Systematic analysis of gene expression in human brains before and after death; Genome Biology 2005, 6:4112.

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